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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,146	05/05/2006	Shyam S. Mohapatra	USF.T193XC1	9945

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/544,146	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,52-59,61,62,64-67 and 69-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,52-55,57-59,61,62,64-67 and 69-77* is/are rejected.

7)☒ Claim(s) *56 and 78* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other. _____.

DETAILED ACTION

An amendment was received and entered on 8/28/09.

Claims 45, 46, 51, 60, 63, and 68 were added and claims 69-78 were added.

Claims 42, 52-59, 61, 62, 64-67, and 69-78 are pending and under consideration.

After further consideration, the enablement rejection is withdrawn. This Action is NON-FINAL in view of the new ground of rejection set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42, 52-55, 58, 59, 64, 69, 71-73, and 75-77are rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002).

Iversen taught methods of inhibiting Dengue virus replication in a human by intravenous administration of an antisense oligonucleotide directed against the Dengue genome. See abstract and paragraphs 34, 36, 40, 50, 153, 154, 158, Example 3, and claim 16.

Raviprakash taught a method of inhibiting expression of DV gene products in mammalian LLCMK/2 cells by microinjection of antisense directed at the 5' end of the

portion of the RNA encoding the structural proteins, and the 3' end of the virus genome. Cells were exposed to DV after delivery of antisense. The target regions were 15 bases in length. One oligonucleotide was directed to a target sequence common to all four DV serotypes. Two oligonucleotides were directed to a non-structural protein (ns5a). See abstract; paragraph bridging pages 69 and 70; first full paragraph on page 70; Fig. 1 on page 70; page 73, column 2, lines 22-26.

Adelman taught a plasmid vector encoding a inverted repeat siRNA directed against Dengue virus structural gene prM RNA, and its use to inhibit DV infection by administration to mosquito cells in vitro. See abstract.

Yu taught expression cassettes encoding hairpin siRNAs and their use in mammalian cells. See abstract. Yu disclosed the concepts of including the cassettes in nonviral vectors and in and viral vectors. See last paragraph on page 6052.

Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

It was clear to those of ordinary skill in the art at the time of the invention that there was interest in inhibiting DV replication in human cells, particularly in view of the teachings of Iversen and Raviprakash, and that RNA interference represented an alternative to antisense methods of gene suppression. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Iversen by substituting an expression vector encoding an shRNA directed

against DV for the antisense oligonucleotide of Iversen. One would have been motivated to do so in order to obtain the advantages disclosed by Tuschl. One of ordinary skill appreciates that shRNAs operate through the same pathway as siRNAs, and would reasonably expect shRNAs to deliver performance superior to that obtained using antisense in view of the teachings of Tuschl. One would have had a reasonable expectation of success because the technology for expressing shRNAs in mammalian cells was available prior to the time of the invention (see Yu above), and there was no reason to doubt that it would have functioned in vivo in human cells.

It would have been similarly obvious to target any of the DV genomic RNA regions set forth by Iversen, Raviprakash, or Adelman because the genome of DV is a positive strand RNA encoding a single polyprotein, such that cleavage of any of the targets would have been expected to inhibit DV replication, particularly those at the 5' genome end, e.g. those directed against prM. One would have been motivated to include expression cassettes for more than one siRNA in order to increase the level of inhibition achieved.

With regard to whether or not the siRNA vector is administered prior to or after DV infection, Iversen taught that treatment could be either prophylactic or post-infection (paragraph 71). In any case, an infected individual will produce infectious virus such that treatment of an infected individual would be considered to result in the treatment of cells that had not yet become infected, but would become infected subsequent to treatment.

Absent evidence to the contrary, delivery to dendritic cells is considered to be inherent in intravenous administration.

Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52-55, 58, 59, 64, 69, 71-73, and 75-77 above, and further in view of Yu et al (US 6852528).

The teachings of Iversen, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

These references do not teach a vector conjugated with chitosan. However, one of ordinary skill appreciates that there is a wide variety of gene delivery techniques which one may employ interchangeably as a matter of design choice. Among these are microinjection (the method used by Raviprakash), lipofection (used by Adelman (2002) and Yu (2002). Yu ('528) also taught that a variety of methods could be used to deliver nucleic acids to cells including microparticle formation with polycations such as chitosan-based compounds, as well as liposome-mediated transfection and microinjection. See column 22, lines 17-44; column 23, lines 30-47; and column 31, lines 22-38. It would have been obvious to one of ordinary skill in the art to select any

of these commonly used transfection techniques, as they were all well recognized in the art as exchangeable alternatives.

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52-55, 58, 59, 64, 69, 71-73, and 75-77 above, and further in view of Kumar et al (US 7067633).

The teachings of Iversen, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

These references do not teach a vector comprising a tissue-specific or inducible promoter.

One of ordinary skill in the art recognizes that particular promoters are selected as a matter of design choice. Inducible and tissue-specific promoters allow one to control the expression of a given construct either through the type of cell used or through the presence or absence of an inducer. For example, Kumar taught that it is important to employ a promoter and/or enhancer that effectively directs the expression of the DNA segment in the cell type, organelle, and organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters enhancers, and cell type combinations for protein expression. Various promoters

employed may be constitutive, tissue specific, inducible and/or useful under the appropriate conditions to direct high level expression of the introduced DNA segment. It would have been obvious to one of ordinary skill in the art to select any of these commonly used promoters based on the need to control expression as a matter of design choice.

Claims 65-67 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52-55, 58, 59, 64, 69, 71-73, and 75-77 above, and further in view of Hope et al (US Patent 6,136,597)

The teachings of Iversen, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

The cited references did not teach adeno-associated virus vectors.

Hope taught that expression cassettes could be delivered by a variety of viral or non-viral vectors, including plasmid, adeno associated virus, adenoviral, retroviral, lentiviral, polioviral and herpes viral vectors. See column 13, line 16, to column 14, line 23. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one

equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. The various vectors described by Hope are all considered to be equivalent platforms for carrying expression cassettes, so it would have been obvious to use any of them to deliver the expression cassette described above. The structural characteristics of the AAV vector of Hope are indistinguishable from those recited in the instant claims, so the functional characteristic of not causing acute inflammation in dendritic cells is considered to be inherent.

Claims 72, 73, 75, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Libraty et al (J. Virol 75(8): 3501-3508, 2001), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002).

Libraty disclosed dendritic cells infected by DV, and indicated that these cells were relevant to understanding the pathogenesis of DV and the development of therapeutic strategies. See abstract.

Raviprakash taught a method of inhibiting expression of DV gene products in mammalian LLCMK/2 cells by microinjection of antisense directed at the 5' end of the portion of the RNA encoding the structural proteins, and the 3' end of the virus genome. Cells were exposed to DV after delivery of antisense. The target regions were 15 bases in length. One oligonucleotide was directed to a target sequence common to all four DV

serotypes. Two were directed to a non-structural protein (ns5a). See abstract; paragraph bridging pages 69 and 70; first full paragraph on page 70; Fig. 1 on page 70; page 73, column 2, lines 22-26.

Adelman taught a plasmid vector encoding a inverted repeat siRNA directed against Dengue virus prM RNA, and its use to inhibit DV infection. See abstract. Adelman indicated that expression from a Sindbis vector of RNA with antisense polarity and that of RNA with sense polarity were equally effective to induce resistance to DEN-2 in mosquito cells and adult mosquitoes, noting that virus resistance had many of the characteristics of RNA silencing, including the presence of Dengue virus-specific siRNA.

Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

Yu taught expression cassettes encoding hairpin siRNAs and their use in mammalian cells. See abstract. Yu disclosed the concepts of including the cassettes in nonviral vectors and in and viral vectors. See last paragraph on page 6052

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cells of Libraty in the experiments of Raviprakash, because Libraty taught that these cells were relevant to understanding the pathogenesis of DV and the development of therapeutic strategies. One of ordinary skill appreciates that gene expression inhibition studies can shed light on the pathogenesis of DV as well as provide information that would be considered useful in the development of therapies,

such as for determining the best genomic target region. It would have been similarly obvious to modify the experiments of Raviprakash to use siRNA expression vectors, such as those taught by Adelman or Yu, instead of antisense oligonucleotides. One would have been motivated to do so in order to obtain the advantages disclosed by Tuschl. One of ordinary skill appreciates that shRNAs operate through the same pathway as siRNAs, and would reasonably expect shRNAs to deliver performance superior to that obtained using antisense in view of the teachings of Tuschl. One would have had a reasonable expectation of success because the technology for expressing shRNAs in mammalian cells was available prior to the time of the invention (see Yu above), and there was no reason to doubt that it would have functioned in human dendritic cells. It would have been similarly obvious to target any of the DV genomic RNA regions set forth by Raviprakash or Adelman because genome of DV is a positive strand RNA encoding a single polyprotein, such that cleavage of any of the targets would have been expected to inhibit DV replication, particularly those at the 5' genome end, e.g. those directed against prM.

Claim 74 is rejected under 35 U.S.C. 103(a) as being unpatentable over Libraty et al (J. Virol 75(8): 3501-3508, 2001), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 72, 73, 75, and 77 above, ad further in view of Hope et al (US Patent 6,136,597).

The teachings of Libraty, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in human blood dendritic cells by administration of a vector encoding an shRNA directed against DV RNA.

The cited references did not teach adeno-associated virus vectors.

Hope taught that expression cassettes could be delivered by a variety of viral or non-viral vectors, including plasmid, adeno associated virus, adenoviral, retroviral, lentiviral, polioviral and herpes viral vectors. See column 13, line 16, to column 14, line 23. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. The various vectors described by Hope are all considered to be equivalent platforms for carrying expression cassettes, so it would have been obvious to use any of them to deliver the expression cassette described above. The structural characteristics of the AAV vector of Hope are indistinguishable from those recited in the instant claims, so the functional characteristic of not causing acute inflammation in dendritic cells is considered to be inherent.

Conclusion

No claim is allowed.

Claims 56 and 78 are objected to because they depend from rejected claims, but would be allowable if rewritten in independent form with all of the limitations of the claims from which they depend.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Tracy Vivlemore, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Richard Schnizer/
Primary Examiner, Art Unit 1635